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REMARKS/ARGUMENTS

Reconsideration of the outstanding Office Action is respectfully requested.

Claims 1-15 remain in this application, although Claims 1 and 3 have been amended. Claims 2 and 4 have been canceled. Claims 16-19 have been previously withdrawn. New Claims 20-25 are added, which are "methods of use" claims for prolonging the therapeutic effect of certain orally administered drugs (claims 20-23) and for treating patients suffered from cancer (claims 24-25). No new matter has been introduced.

Applicants acknowledge the Examiner's withdrawal from consideration of Claims 16-19, in the absence of an allowable linking claim(s). Applicants expressly submit that they reserve any right to file continuing application(s) directed to any non-elected subject matter or request a reunion of the non-elected claims with the elected claims upon allowance of this application.

Applicants respectfully submit that the amendments have overcome the rejections for reasons set forth below:

Claim Rejections Under 35 U.S.C. §103(a)

In the Office Action dated May 29, 2003, Claims 1-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,229,116 to Edgar et al. ("the '116 Patent"), U.S. Patent No. 6,180,666 to Wacher et al. ("the '666 Patent"), U.S. Patent No. 6,028,054 to Benet et al. ("the '054 Patent"), and U.S. Patent No. 6,121,234 to Benet et al. ("the '234 Patent").

As a preliminary matter, first, it is noted that none of the above cited prior art teaches the use of a CYP3A inhibitor to treat patients suffered from cancer, particularly intestinal or hepatic

cancer. Thus, new claims 25-26, which are "method of use" claims for treating patients suffered from cancer, are clearly not obvious over the cited prior art. Secondly, it is noted that none of the cited prior art, individually or in any combination, has disclosed that any of the claimed CYP3A inhibitors in new claim 20 can prolonged the therapeutic effect of certain orally administered drug also claimed in claim 20, namely, erythromycin, troleandomycin, teffenadine, tamoxifen, lidocaine, triazolam, dapsone, diltiazem, lovastatin, simvastatin, quinidine, midazolam, and alfentanil. Thus, new claims 20-23 are not obvious over the cited prior art. Finally, Applicants would like to draw the Examiner's attention to claim 11, which specifically cites a co-administration of CYP3 inhibitor catechin and a first-pass effect drug simvastatin. The specific effect of catechin in prolonging the therapeutic effect of simvastatin is particularly shown in Figures 1 and 2. It is noted that none of the cited prior art has taught, either individually or in any combination, this specific effect of catechin. Thus, claim 11 is definitely not obvious over the teachings of the prior art.

With respect to caims 1-15, Applicants respectfully traverse the rejections under 35 U.S.C. § 103(a), as being unpatentable over the '116 Patent, the '666 Patent, the '054 Patent, and the '234 Patent, and request reconsideration with respect to these pending claims.

In particular, Applicants have amended claim 1 to remove certain cytochrome 450 3A (CYP3A) inhibitors so that the claimed invention is distinguishable from the teachings in the cited prior art. As a result, the amended claim 1 is non-obvious over the cited references for reasons set forth below:

> The teaching or suggestions to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not

> based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. **Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.** The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The grounds of rejection do not establish a *prima facie* case of obviousness because the applied references, neither individually nor taken in combination, suggest Applicants' amended claims.

The '116 Patent discloses a method to increase the bioavailability of pharmaceutical agents susceptible to oxidation of cytochrome P450 by administering certain flavonoids in the aglycone or glycoside form. The pharmaceutical agents which are oxidized by cytochrome P-450 include anti-hypertensive agents of the dihydropyridine type, cyclosporine, and steroids, e.g., cortisone. See Column 1, lines 9-12 of the '116 Patent. The specific flavonoids that can improve the bioavailability of the specific pharmaceutical agents are listed in Table 1 of the '116 Patent.

The '666 Patent discloses the use of gallic acid esters as inhibitors of CYP 3A in the gut to increase bioavailability of oral pharmaceutical compositions. However, the '666 Patent does not mention gallic acid, the salts of gallic acid, or any of the other compounds claimed in the amended Claim 1 of the instant application.

The '054 Patent discloses a method for increasing bioavailability of an oral pharmaceutical compound by concurrent administration of CYP 3A inhibitors or substrates.

Table I of the '054 Patent discloses forty CYP 3A inhibitors or substrates, but fails to teach any of the compounds of instant invention as set forth in the amended claim 1.

The '234 Patent discloses a method for increasing bioavailability of an oral pharmaceutical compound by concurrent administration of essential oil and essential oil component. It provides a list of 73 essential oils (Table 1) and a list of 47 essential oil components (Table 2). Moreover, the '234 Patent (column 18, lines 47-49) teaches that "[s]ome essential oils reduce CYP3A drug biotransformation by acting either as an inhibitor of CYP3A activity or as a substrate of CYP3A activity." (*Emphasis added.*) However, the '234 Patent fails to describe Applicants' claimed invention.

In Applicants' view, the rejections of the claims over the four references, individually or in combination, fail to establish a *prima facie* case of obviousness. Even in combination, the references fail to describe the elements of Applicants' claims. The old maxim, "obviousness cannot be predicated on the unknown" appears to control here. Withdrawal of the rejections asked on the four references is respectfully solicited.

No Suggestion Or Motivation to Combine Prior Art References

As aforementioned, each cited reference discloses distinctly different and unrelated types of compounds, *i.e.*, the '116 Patent discloses certain flavonoids, the '666 Patent discloses gallic acid esters, and the '234 Patent discloses the essential oils and essential oil components. None of the cited references refers to the other types of compounds disclosed in other references. As to

the '054 Patent, it does not disclose any of the compounds set forth in the amended claim 1. Therefore, there can be no motivation nor suggestion in the references to combine the teachings, particularly when one considers that each prior art reference discloses large numbers of compounds, and yet there is no overlapping of compounds disclosed or suggested among the prior art references.

Thus, the Examiner's combination of the cited references must be derived from the use of hindsight, *i.e.*, to rely on Applicants' claimed invention as a blueprint in order to seek out the references, instead of relying on the natural teachings of the prior art references. It would be impossible, especially when the cited references do not provide a clear teaching even for compounds within its own references, *infra*. But hindsight is not a basis for obviousness.

In summary, there was no suggestion or motivation for those skilled in the art to combine the prior art references.

No Reasonable Expectation of Success

The Patent and Trademark Office has relied upon no evidence to assert that the references provide a reasonable expectation of success. And there is none. At most, the '116 Patent might be within the classic example of "obvious to try" and would only be applicable to the flavonoids, not other types of compounds. The Federal Circuit has always taken the position that "obvious to try" is not a basis for obviousness under 35 U.S.C. § 103. *See, Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725, 16 U.S.P.Q.2d 1923, 1928 (Fed. Cir. 1990), *In re Eli Lilly & Co.*, 14 U.S.P.Q.2d 1741 (Fed. Cir. 1990), *In re O'Farell*, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988).

> "There is usually an element of 'obviousness to try' in any research endeavor, that it is not undertaken with complete blindness but rather with some semblance of a chance of success, and that patentability determinations based on that as the test would not only be contrary to statute but also result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of 'research'." *In re Tomlinson*, 150 U.S.P.Q. 623,626 (CCPA 1966).

Even if the "obvious to try" doctrine is found not to be applicable in the present case, as shown in the amended claim 1, the compounds that are considered to be aglycone or glycoside form of a flavonoid have been deleted from the claimed invention. Thus, the obviousness rejections over the '116 patent are moot.

As for the '666 Patent, it discloses the gallic acid esters specifically, but there is no teaching or suggestion to indicate whether gallic acid itself or its salts will inhibit the CYP 3A. In order to expedite the allowance of the present case, Applicants are willing to delete gallic acid from being considered in the present application. Thus, the obviousness rejections over the '666 patent are also moot.

The '234 Patent discloses more than 100 essential oils and essential oil components (listed in Tables 1 and 2), which can be CYP3A inhibitors or CYP3A substrates or neither. That disclosure expresses no prediction concerning the behavior of undisclosed compounds. In order to expedite the allowance of the present case, Applicants are willing to delete β-myrcene, terpineol, and trans-cinnamaldehyde from being considered in the present application. Thus, the obviousness rejections over the '666 patent are also moot.

As for the '054 Patent, it does not disclose any of the compounds of the instant application, and thus cannot provide those skilled in the art any reasonable expectation on any of the compounds.

In summary, the cited references (alone or even if they can be combined) do not provide those skilled in the art any reasonable expectation of success even for compounds referenced within the references, let alone for expectation on a different type of compounds listed in a different reference.

Applicants respectfully request withdrawal of the rejections.

Reconsideration and an early allowance are respectfully solicited. Should the application not be passed to issuance, the Examiner is requested to contact the Applicant's attorney to resolve the problem.

Respectfully submitted,

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